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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/775,678	FIGURA ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2009 and 17 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-115* is/are pending in the application.

4a) Of the above claim(s) *91,97,99,100,106,112,114 and 115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-90,92-96,98,101-105,107-111 and 113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/12/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 86-115 are pending in the application.

[2] Applicants' amendment to the claims, filed on 1/14/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicants' amendment to the specification, filed on 3/17/08, is acknowledged.

[4] Receipt of an information disclosure statement filed on 5/12/08, is acknowledged.

[5] Applicant's remarks filed on 3/17/08 in response to the Office action mailed on 9/17/07 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[7] Initially, it is noted that the examiner inadvertently excluded claims 107-108 from the claim groupings and indicated that these claims are withdrawn in the restriction requirement mailed on 8/1/08. However, these claims, being dependent from claim 101, should have been included with the claims of Groups I, II, III, and IV of the 8/1/08 restriction requirement.

[8] Applicant's election without traverse of Group II, claims 86-90, 92-96, 98, 101-105, 107-111, and 113, in the reply filed on 9/2/08, is acknowledged. Applicant's further

election of sulfatase species 1) Iduronate 2-Sulfatase in the reply filed on 9/2/08 is acknowledged.

[9] Claims 91, 97, 99-100, 106, 112, and 114-115 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

[10] Claims 86-90, 92-96, 98, 101-105, 107-111, and 113 are being examined in the merits. Claims 96 and 111 are being examined only to the extent the claims read on the elected subject matter.

Information Disclosure Statement

[11] All references cited in the information disclosure statement (IDS) filed on 5/12/08 have been considered by the examiner. A copy of Form(s) PTO/SB/08 is attached to the instant Office action.

Claim Objection

[12] Claim 101 is objected to in the recitation of "an amino acid sequence that is at least 95% identical to SEQ ID NO:2" and in order to improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.,* "an amino acid sequence that has at least 95% identity to the amino acid sequence of SEQ ID NO:2".

Claim Rejections - 35 USC § 112, Second Paragraph

[13] The rejection of claims 86-90 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of the relative phrases "a sulfatase with an increased expression" and "a Formylglycine Generating Enzyme with an increased expression" is withdrawn in view of the amendment to claim 86 to recite a reference level of expression.

[14] Claim(s) 86-90, 92-96, 98, 101-105, 107-111, and 113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

[a] Claims 86 (claims 87-90, 92-96, and 98 dependent therefrom) and 101 (claims 102-105, 107-111, and 113 dependent therefrom) are indefinite in the recitation of "the sulfatase is an activated form of an endogenous sulfatase" and "the Formylglycine Generating Enzyme is an activated form of an endogenous Formylglycine Generating Enzyme" because it is unclear as to the intended meaning of "activated". For example, is the term intended as being interpreted as meaning a enzymatically active form of the respective polypeptide as suggested by the preamble's use of the term "active"? Does the "activated form" require some modification(s) to SEQ ID NO:2? Alternatively, the specification suggests that the term "activate" also includes the meaning "insertion of strong promoter" (p. 11, lines 23-26). It is suggested that applicant clarify the meaning of the claims, particularly with respect to the meaning of the term "activated form".

[b] Claim 101 (claims 102-105, 107-111, and 113 dependent therefrom) is indefinite in the recitation of "stringent conditions (6X SSC at 65°C)" because it is unclear as to whether the text in parentheses, *i.e.*, 6X SSC at 65°C, is intended as being *the* stringent conditions or the text in parentheses is merely exemplary of conditions that are encompassed by "stringent conditions". It is suggested that applicant clarify the meaning of the claim, particularly with respect to the phrase "stringent conditions (6X SSC at 65°C)".

Claim Rejections - 35 USC § 101

[9] Claim(s) 86-90, 92-96, 98, 101-105, 107-111, and 113 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to sulfatase-producing cells. The claim(s) read on a product of nature and should be amended to indicate the hand of the inventor, e.g., by insertion of "purified" or "isolated" with respect to the claimed cell. See MPEP § 2105.

RESPONSE TO ARGUMENT: At p. 10 of the instant remarks, applicant argues that since a cell expressing an "activated form" of an FGE or an exogenous FGE is not naturally occurring, the claims do not read on a product of nature.

Applicant's argument is not found persuasive. As noted above, it is unclear as to applicant's intended meaning of the phrase "activated form" and when the phrase is interpreted as meaning an enzymatically active form, the claims read on a product of nature and should be amended to indicate the hand of the inventor.

Claim Rejections - 35 USC § 112, First Paragraph

[15] Claims 86-90, 92-96, 98, 101-105, 107-111, and 113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

The claims are drawn to a genus of sulfatase-producing cells, wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased and the cell comprises: 1) a sulfatase, wherein the sulfatase is an "activated form" of an endogenous sulfatase or an exogenous sulfatase, wherein the expression is increased by any method or mechanism and 2) a Formylglycine Generating Enzyme (FGE) with an increased expression, wherein the FGE is an "activated form" of an endogenous SEQ ID NO:2 or an ortholog thereof or an exogenous FGE or an ortholog thereof, wherein the expression is increased by any method or mechanism.

The term "ortholog" in claim 86 has been broadly, but reasonably interpreted as meaning a polypeptide that has formyl-glycine generating enzymatic activity. The phrase "an amino acid sequence that is encoded by a nucleic acid..." in claim 101, part (b) has been broadly, but reasonably interpreted as any two contiguous amino acids that are encoded by the recited nucleic acid and thus encompasses an FGE comprising any two contiguous amino acids encoded by the recited nucleic acid. As noted above, it is unclear as to applicant's intended meaning of the phrase "activated form" and the phrase can be interpreted as meaning a modified form of a sulfatase or an FGE as recited in the claims. In view of these interpretations, the genus of FGE polypeptides is essentially unlimited.

Also, the phrase "an amino acid sequence that is encoded by a nucleic acid..." in claim 101, part (b) has been broadly, but reasonably interpreted as any two contiguous amino acids that are encoded by the recited nucleic acid and thus encompasses an FGE having, *i.e.,* comprising, any two contiguous amino acids encoded by the recited nucleic acid. Also, it is noted that the recited hybridization conditions do not require hybridization over the full length of the "complement" and do not require a wash step. Thus, an FGE-encoding nucleic acid comprising any two contiguous nucleotides, *i.e.,* a nucleic acid, that hybridize under the recited conditions to the recited complement satisfy the structural requirement of part (b) of claim 101.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings,

or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Sufficient description to show possession of such a genus "may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification discloses only the following representative species of the recited genus of sulfatase-producing cells: an isolated host cell transformed with an expression vector encoding a sulfatase polypeptide and encoding the FGE polypeptide of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the sulfatase. In this case, the species encompassed by the genus are widely variant, including species having any structure

from any source and any variants thereof. As such, the genus encompasses widely variant species, wherein the disclosed species fail to reflect the variation among the members of the genus. Given the lack of description of a representative number of peptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

With the exception of claims 98 and 113, the claims recite only functional features of the genus of each of the sulfatase and FGE of the sulfatase-producing cells. However, this recitation fails to provide a sufficient description of the claimed genus of cells as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "[i]n claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the claimed genus of sulfatase-producing cells, the functional definition of the genus does not provide any structural information commonly possessed by members of the

genus which distinguish the species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) further stated: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus". Even with claims 98 and 113, which require the FGE to comprise a subdomain 3, which comprises SEQ ID NO:79, this shared structural feature does not constitute a "substantial portion of the genus".

Moreover, the disclosed representative species fail to support an adequate description of the recited genus because there is no correlation between the structures of the species and the function of modifying a catalytic cysteine to a formylglycine of the encoded sulfatase. Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

Accordingly, for at least the reasons stated above, it is the examiner's position that the specification fails to adequately describe the claimed invention.

RESPONSE TO ARGUMENT: Beginning at p. 10 of the instant remarks, applicant argues the claims have been amended to require the cell to express the FGE of SEQ ID NO:2 or an ortholog thereof. According to applicant, the specification discloses a representative number of "orthologs" of SEQ ID NO:2 and discloses relevant identifying structural features of such orthologs to show possession of the genus.

Applicant's argument is not found persuasive. For at least the reasons set forth above, the examiner maintains the position that the specification fails to adequately describe the genus of sulfatase-producing cells.

[16] Claim(s) 86-90, 92-96, 98, 101-105, 107-111, and 113 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated sulfatase-producing cell transformed with an expression vector encoding a sulfatase polypeptide and encoding the FGE polypeptide of SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, wherein the FGE polypeptide modifies a catalytic cysteine to a formylglycine of the encoded sulfatase such that the ratio of active sulfatase to total sulfatase produced by the cell is increased up to 100% over the ratio of active sulfatase to total sulfatase produced by the cell in the absence of FGE, does not reasonably provide enablement for all sulfatase-producing cells as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors considered to be most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims…and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims" (citation omitted) and "[w]hen analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification."

As noted above, the claims are drawn to a sulfatase-producing cell, wherein the ratio of active sulfatase to total sulfatase produced by the cell is increased and the cell comprises: 1) a sulfatase, wherein the sulfatase is an "activated form" of an endogenous sulfatase or an exogenous sulfatase, wherein the expression is increased by any method or mechanism and 2) a Formylglycine Generating Enzyme (FGE) with an increased expression, wherein the FGE is an "activated form" of an endogenous SEQ ID NO:2 or an ortholog thereof or an exogenous FGE or an ortholog thereof, wherein the expression is increased by any method or mechanism.

The term "ortholog" in claim 86 has been broadly, but reasonably interpreted as meaning a polypeptide that has formyl-glycine generating enzymatic activity. The phrase "an amino acid sequence that is encoded by a nucleic acid..." in claim 101, part (b) has been broadly, but reasonably interpreted as any two contiguous amino acids that are encoded by the recited nucleic acid and thus encompasses an FGE comprising any two contiguous amino acids encoded by the recited nucleic acid. As noted above, it is unclear as to applicant's intended meaning of the phrase "activated form" and the phrase can be interpreted as meaning a modified form of a sulfatase or an FGE as recited in the claims. In view of these interpretations, the genus of FGE polypeptides is essentially unlimited.

The phrase "an amino acid sequence that is encoded by a nucleic acid..." in claim 101, part (b) has been broadly, but reasonably interpreted as any two contiguous amino acids that are encoded by the recited nucleic acid and thus encompasses an FGE having, *i.e.*, comprising, any two contiguous amino acids encoded by the recited

nucleic acid. Also, it is noted that the recited hybridization conditions do not require hybridization over the full length of the "complement" and do not require a wash step. Thus, an FGE-encoding nucleic acid comprising any two contiguous nucleotides, *i.e.*, a nucleic acid, that hybridize under the recited conditions to the recited complement satisfy the structural requirement of part (b) of claim 101.

As noted above, the cell is not "isolated" or "purified" and thus encompasses a naturally occurring cell or a cell within, *e.g.*, a transgenic animal, in accordance with the specification at p. 39, bottom.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The amino acid sequence of a polypeptide determines its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.*, multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled

artisan would recognize the high level of unpredictability associated with altering the amino acid sequence of a polypeptide.

The state of the art provides evidence for the high degree of unpredictability in altering a polypeptide sequence with an expectation that the altered polypeptide will have the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991; cited in a prior Office action) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability… …they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). Further, Dierks et al. (*Cell* 113:435-444, 2003; cited in the IDS filed on 2/28/05) teaches that even single amino acid mutations in the *SUMF1* gene, which encodes human FGE, result in multiple sulfatase deficiency, which is characterized by a catalytically inactive FGE polypeptide (pp. 438-439). See also MPEP 2144.08.II.A.4.(c), which states, "[t]he effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell *et al.*, *Molecular Cell Biology* 51(2d ed. 1990)." Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining

a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide. Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses the following working examples of FGE polypeptides: SEQ ID NO:2, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, or 78, and only a single method for overexpressing sulfatase and FGE polypeptides, *i.e.*, transformation of a host cell with an expression vector encoding the sulfatase and FGE polypeptides. Also, the references of Szameit et al. (*J. Biol. Chem.* 274:15375-15381, 1999) and Rommerskirch et al. (*PNAS* 89:2561-2565, 1992) disclose sulfatase-producing cells within the scope of the claims. While the specification provides additional *general* guidance, the specification fails to provide any additional *specific* guidance regarding those amino acids of an FGE polypeptide that can be altered with an expectation of maintaining the ability to modify a sulfatase catalytic cysteine to a formylglycine. Further, the specification fails to provide any specific guidance for modifying a cell to achieve overexpression of a sulfatase and an FGE.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: It was not routine in the art at the time of the invention to screen for any FGE as broadly encompassed by the claims for those that have the

ability to maintain activity of modifying a sulfatase catalytic cysteine to a formylglycine and to overexpress this FGE along with any sulfatase in a host cell by any method of overexpression as broadly encompassed by the claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation that is required, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: Beginning at p. 15 of the instant remarks, applicant argues the claims have been amended to require the cell to express the FGE of SEQ ID NO:2 or an ortholog thereof. According to applicant, the teachings of the specification in view of the state of the art at the time of the invention enables the full scope of the clamed sulfatase-producing cells.

Applicant's argument is not found persuasive. For at least the reasons set forth above, the examiner maintains the position that the specification fails to enable the full scope of sulfatase-producing cells.

Claim Rejections - 35 USC § 102/103

[17] Claim(s) 86-90, 92, 101-105, and 107 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Szameit (reference U of Form PTO-892 mailed on 9/17/07) as evidenced by Fang (reference W of Form PTO-892 mailed on 9/17/07) and as evidenced by GenBank Accession Number AJ131525 (April 1999; hereafter referred to as "AJ131525"). According to MPEP 2112.III, "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977)." MPEP 2112.IV states, "'[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.' *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)."

CLAIM INTERPRETATION: As noted above, the term "ortholog" in claim 86 has been broadly, but reasonably interpreted as meaning a polypeptide that has formyl-glycine generating enzymatic activity. The phrase "an amino acid sequence that is encoded by a nucleic acid..." in claim 101, part (b) has been broadly, but reasonably interpreted as any two contiguous amino acids that are encoded by the recited nucleic acid and thus encompasses an FGE having, *i.e.,* comprising, any two contiguous amino acids encoded by the recited nucleic acid. Also, it is noted that the recited hybridization conditions do not require hybridization over the full length of the "complement" and do not require a wash step. Thus, an FGE-encoding nucleic acid comprising any two contiguous nucleotides, *i.e.,* a nucleic acid, that hybridize under the recited conditions to the recited complement satisfy the structural requirement of part (b) of claim 101.

The reference of Szameit teaches *Klebsiella pneumoniae atsA* gene encodes a sulfatase polypeptide that requires co-expression of *K. pneumoniae atsB* gene for catalytic activity, wherein co-expression of the *atsA* and *atsB* genes in *E. coli* "led to production of high sulfatase activity" (p. 13575, abstract; p. 15376, Figure 2), wherein Figure 2 shows the activity of the *K. pneumoniae* sulfatase in an *E. coli* co-expressing both *atsA* and *atsB* genes is increased "at least 100%" over an *E. coli* where *atsB* gene is not expressed. The reference teaches co-expression of *K. pneumoniae atsA* and *atsB* genes in an *E. coli* expression host (p. 15376, column 1, middle) results in formylglycine modification of serine at position 72 of the *atsA* gene product (p. 15375, abstract).

According to MPEP 2131.01.III, a multiple reference 35 U.S.C. 102 rejection is proper where the extra reference is used to "[s]how that a characteristic not disclosed in

the reference is inherent" and that "the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. See MPEP § 2124." Evidentiary reference Fang is cited to show that AtsB of *Klebsiella pneumoniae* is an FGE. According to Fang, "AtsB of *Klebsiella pneumoniae* is directly involved in [formylglycine] generation from serine…It is concluded that AtsB oxidizes serine to [formylglycine]" (p. 14570, abstract). Since both SEQ ID NO:2 and the FGE of Szameit have formyl-glycine generating enzymatic activity, the FGE of Szameit has been interpreted as being an "ortholog" of SEQ ID NO:2. This anticipates claims 86-90 and 92 as written.

Evidentiary reference AJ131525 is cited as showing that the FGE encoded by *Klebsiella pneumoniae atsB* comprises at least two amino acids encoded by the nucleic acid as recited in claim 101, part (b). For example, amino acids 5-6 of the FGE encoded by *Klebsiella pneumoniae atsB* are Ala-Ala, which is the same as amino acids 2-3 of SEQ ID NO:2 herein. This anticipates 101-105 and 107 as written.

RESPONSE TO ARGUMENT: Beginning at p. 21 of the instant remarks, applicant argues that since the FGE of Szameit modifies a serine instead of a cysteine residue, it is not encompassed by the FGE of the claims.

Applicant's argument is not found persuasive. Claim 86 recites "an exogenous Formylglycine Generating Enzyme of SEQ ID NO:2 or an ortholog thereof", which, according to applicant, an ortholog of SEQ ID NO:2 modifies cysteine, not serine. However, contrary to applicant's assertion, there is no limiting definition of an "ortholog" in the specification that requires an ortholog of SEQ ID NO:2 to modify only cysteine residues to the exclusion of modifying serine residues. Also, there is no limitation in the

claims that requires an "ortholog" of SEQ ID NO:2 to modify *only* cysteine residues. As such, to interpret the term "ortholog" as being limited only to those FGE polypeptides that modify cysteine residues would improperly import claim limitations from the specification. See MPEP 2111.01.II. In accordance with MPEP 2111, the examiner has broadly, but reasonably interpreted the term "ortholog" with respect to the FGE of SEQ ID NO:2 as encompassing a protein that has formyl-glycine generating enzymatic activity, regardless of whether the modified residue is a cysteine or a serine. In this case, since both SEQ ID NO:2 and the FGE of Szameit have formyl-glycine generating enzymatic activity, the FGE of Szameit has been interpreted as being an ortholog of SEQ ID NO:2. As such, the cell of Szameit is encompassed by the claims.

[18] Claim(s) 86-90, 93-96, 98, 101-105, 108-111, and 113 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rommerskirch (reference U of Form PTO-892 mailed on 9/17/07) as evidenced by Dierks (cited in the IDS filed on 2/28/05) and as evidenced by Wraith (*Hum. Genet.* 87:205-206, 1991; hereafter referred to as "Wraith"). The claims have been broadly, but reasonably interpreted as noted above. Also, as noted above, it is unclear as to applicant's intended meaning of the phrase "activated form" the phrase has been reasonably interpreted as meaning an enzymatically active form.

The reference of Rommerskirch teaches a comparison of steroid sulfatase (STS) mRNA in control human fibroblasts and human chromosome X-linked-ichthyosis fibroblasts (p. 2562, Figure 1). According to the reference, "[i]n total RNA of

controls…the STS probe detects RNA species…[i]n total RNA from fibroblasts carrying a deletion of the STS gene (X-linked ichthyosis), none of the STS RNA species is detectable" (p. 2562, column 1, bottom and p. 2562, column 2, top). The reference teaches a comparison of STS enzymatic activities in control fibroblasts and chromosome X-linked-ichthyosis fibroblasts (p. 2563, Table 3). According to Table 3, the STS activity in control fibroblasts is 1.4 nmol/hr/mg and 0.05 nmol/hr/mg for chromosome X-linked-ichthyosis fibroblasts (p. 2563). The results of Rommerskirch demonstrate that normal human fibroblasts have increased expression of STS relative to chromosome X-linked-ichthyosis fibroblasts. Rommerskirch further teaches a comparison of STS enzymatic activities in control fibroblasts and multiple sulfatase deficiency (MSD) fibroblasts (p. 2563, Table 3). According to Table 3, the STS activity in control fibroblasts is 1.4 nmol/hr/mg and <0.05 nmol/hr/mg for MSD fibroblasts (p. 2563), wherein 1.4 nmol/hr/mg is an increase of "at least 100%" over <0.05nmol/hr/mg.

According to evidentiary reference Dierks, "C_α-formylglycine (FGly) is the catalytic residue in the active site of eukaryotic sulfatases. It is posttranslationally generated from a cysteine in the endoplasmic reticulum. The genetic defect of FGly formation causes multiple sulfatase deficiency (MSD)" (p. 435, "Summary" section). Dierks provides evidence that MSD fibroblasts are defective in FGE activity (p. 440, Table 2), wherein complementation of MSD fibroblasts with DNA encoding FGE enhanced STS activity, albeit to a lower level than normal fibroblasts. As shown by evidentiary reference Dierks, normal human fibroblasts appear to have increased expression of catalytically active FGE relative to MSD fibroblasts. Since the normal

fibroblasts and the MSD fibroblasts are both fibroblasts, they are considered to be of the same cell type. Also, Dierks discloses that human FGE is expressed in fibroblasts (p. 437, column 2, bottom) and has a domain 3 sequence NH_3-RVKKGGS-COO^- (p. 437, Figure 3, amino acids 327 to 333) and thus satisfies the FGE structural requirements of claims 98 and 113.

Evidentiary reference Wraith teaches cultured fibroblasts with a complete deletion of the iduronate-2-sulfatase (IDS) gene (p. 205, abstract and p. 206, Figure 1 caption), where the normal fibroblasts of Rommerskirch and the fibroblasts of Wraith are both of the same cell type and since an IDS gene is deleted in the fibroblasts of Wraith, the normal fibroblasts of Rommerskirch necessarily have increased expression of iduronate-2-sulfatase relative to the fibroblasts of Wraith, thus satisfying the limitations of claims 96 and 111.

The normal human fibroblasts of Rommerskirch anticipate the claimed sulfatase-producing cell since: 1) Rommerskirch teaches normal human fibroblasts have increased expression of STS relative to chromosome X-linked-ichthyosis fibroblasts; 2) Rommerskirch teaches normal human fibroblasts have increased STS activity relative to MSD fibroblasts, which, as evidenced by Dierks, are defective in FGE activity and thus normal human fibroblasts have increased expression of FGE relative to MSD fibroblasts"; and 3) MSD fibroblasts are defective in FGE and exhibit <0.05nmol/hr/mg STS activity relative to normal human fibroblasts that produce FGE and exhibit 1.4 nmol/hr/mg STS activity is evidence that normal human fibroblasts have active sulfatase

activity that is 100% greater than sulfatase activity of human fibroblasts in the absence of FGE. This anticipates claims 86-90, 93-96, 98, 101-105, 108-111, and 113 as written.

RESPONSE TO ARGUMENT: Beginning at p. 22 of the instant remarks, applicant argues that since the FGE of Rommerskirch is neither "activated" nor exogenous, it is not encompassed by the FGE as recited in the claims.

Applicant's argument is not found persuasive. As noted above, it is unclear as to applicant's intended meaning of the phrase "activated form" and the phrase is interpreted herein as meaning an enzymatically active form. As such, an endogenous FGE polypeptide of the normal human fibroblasts of Rommerskirch, which according to evidentiary reference Dierks have FGE enzymatic activity, the normal human fibroblast of Rommerskirch is considered to have an FGE in an "activated form".

Conclusion

[19] Status of the claims:

- Claims 86-115 are pending.
- Claims 91, 97, 99-100, 106, 112, and 114-115 are withdrawn from consideration.
- Claims 86-90, 92-96, 98, 101-105, 107-111, and 113 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656